

REMARKS/ARGUMENTS

By this amendment a number of claims are canceled and the focus is now on claim 20 as the main claim to be prosecuted in this application. Cancellation of claims and limitation of claim 20 as amended is done without prejudice to Applicants' right to continue seeking canceled or broader claims in a subsequent continuing application or the like.

All claims being prosecuted in this application are limited to kits for detecting at least four cytokines, using a diluent lacking in said cytokines and solid supports differentiable by a differentiation parameter into subgroups, each subgroup of solid supports having immobilized thereon a capture reagent for a particular cytokine sought to be identified.

Support for the kit being suitable to identify four or more cytokines is found in the specification on page 2 line 21.

Claims 100-102 define a kit in which the diluent is selectively substantially free of the four or more cytokines in question. The term "selectively substantially free" is meant to indicate that the diluent can, and generally will, contain other cytokines normally present in such a serum or plasma sample, and that only the cytokines to be analyzed for are lacking in that serum or plasma. The specification clearly indicates, for example in its discussion of removal of cytokines by affinity chromatography, that only those cytokines to be analyzed for are removed by this technique, by implication leaving others remaining in that fluid. In general, it is well known that a subject's blood can contain a great many cytokines, and this is pointed up by the fact that the specification states that the diluent can be lacking in up to 50 different cytokines. Accordingly, while the term "selectively substantially free" is not used per se in the specification, the concept this term represents is clearly present there, and those skilled in the art would understand, from reading the specification, that the inventor had possession of this concept when the application was filed.

If the examiner agrees that this concept is contained in the specification but that alternative language would be more appropriate, he is encouraged to call the undersigned attorney.

Claims 20 and those following provide a kit for conducting multiplex analysis for four or more cytokines in a serum or plasma sample of a patient or subject. That kit contains three major components:

One or more concentrated materials that collectively or separately contain the four or more cytokines sought to be determined;
a set of solid supports (preferably particles) that are differentiable into four or more subgroups (the number of subgroups corresponding to the number of cytokines to be analyzed for), each subgroup having an immobilized capture reagent for a certain cytokine among those to be analyzed for;
and a standard diluent that comprises serum or plasma (accordingly) that is substantially free of the four or more cytokines to be analyzed.

The provision of such a diluent in a kit of this type, in combination with the concentrated materials and the differentiable solid supports, enables a multiplex analysis for the four or more cytokines to be carried out using only a single standard diluent as opposed to having (as is otherwise the practice) a set of diluents, one for each cytokine to be determined.

The diluent does not have to be prepared by synthetic or artificial methods but is obtained either from a population whose blood or serum naturally lacks the four or more cytokines in question, or by removing them from serum or plasma samples using affinity chromatography.

In the previous rejection, claims were rejected over a combination of Williams et al. in view of Boguslaski et al.

Williams et al., however, deal only with the removal of all steroids in a sample in order to prevent interference with a steroid. The reference has no relevance to kits for use in multiplex analyses for cytokines and, in addition, Williams et al. wish to avoid use of plasma in their work (col. 3 line 62-64) whereas the claimed kits may contain plasma-based materials

Boguslaski et al. is relied on only for its general disclosure of providing kits, and otherwise has no relevance to Williams et al. or to the claimed invention.

Applicants respectfully request withdrawal of the rejection of claims as obvious over Williams et al. and Boguslaski et al.

Claims were also rejected as obvious over a combination of Tamarkin et al. and Williams et al. Tamarkin et al. is emblematic of the prior art in that the reference discloses a diluent lacking only a single analyte. A series of diluents according to Tamarkin et al. would be required for any multiplex analysis. The examiner asserted that those skilled in the art would be led to combine the teachings of Williams et al. with those of Tamarkin et al. to produce a kit as claimed.

However, those skilled in the art would not make this combination. The two references relate to diluents and kits for two totally distinct and unrelated purposes. Tamarkin et al. involve measuring cytokines in blood. Williams et al., on the other hand, is directed to finding storage-stable calibrator and control solutions for steroid immunoassays. Each reference relates to different technology and different types of analytes, and to different purposes, and those skilled in the art would not lift some particular feature from one (such as the point in Williams et al. that all steroids can be removed from the solution) and apply it to the other, which is directed to a different issue and solves a different problem. The combination proposed by the examiner is not one that would have been made by those skilled in the art looking to provide improved standard diluents for multiplex assays.

In addition, nothing in Tamarkin et al. would indicate that their single-analyte standard diluents could be expanded to allow for simultaneous use with four or more cytokines.

Applicants respectfully request withdrawal of the rejection of claims based on the combination of Tamarkin et al. and Williams et al.

Claims also were rejected over the combination of Tamarkin et al. and Williams et al., further in view of Posner et al. The addition of Posner et al. does not change the point that those skilled in the art would not make the Tamarkin et al./Williams et al. combination, as discussed above.

Applicants respectfully request withdrawal of the rejection of claims over the three-reference combination of Tamarkin et al., Williams et al. and Posner et al.

Claims were rejected over the combination of Tamarkin et al. and Williams et al. further in view of Oliver et al.

Oliver et al. is cited for the disclosure of differentially stained particles in assays wherein the particles comprise immobilized capture reagents. Applicants do not claim to have invented such systems. Oliver et al. is a brief disclosure of the use of Luminex® bead systems for multiplex analysis and determination of a plurality of cytokines. Interestingly enough, though Oliver et al. do mention calibrators and diluents, they do not disclose the use of a single standard diluent lacking two or more, least of all four or more, cytokines or other analytes. This total lack points up the unobviousness of Applicants' invention (of course, it is true that such a disclosure might have been a basis for an anticipation as opposed to obviousness rejection, still the lack of it, where it might have been expected, Applicants submit, supports the unobviousness of the present invention).

Applicants respectfully request withdrawal of rejections of claims over the combination of Tamarkin et al., Williams et al. and Oliver et al.

Claims were rejected as obvious over the combination of Oliver et al. and Boguslaski et al. As above, neither reference discloses a single diluent lacking in multiple cytokines.

Applicants respectfully request withdrawal of this rejection.

Claims were rejected as obvious over the combination of Tamarkin et al. and Williams et al., further in view of Vignali. The last-mentioned reference discloses detection of multiple cytokines but fails to disclose use of a single diluent. Again, this striking omission shows the unobviousness of the claimed invention.

Applicants respectfully request withdrawal of the rejection of claims over the combination of Tamarkin et al., Williams et al. and Vignali.

Claims also were rejected as obvious over Oliver et al, and Boguslaski et al. in view of Vignali.

For reasons mentioned above, this rejection is untenable and Applicants respectfully request its withdrawal.

Appl. No. 10/017,788
Amdt. dated November 27, 2006
Amendment under 37 CFR 1.116 Expedited Procedure
Examining Group 1641

PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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